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Drugs used during the COVID-19 first wave in Vitoria-Gasteiz (Spain) and their presence in the environment

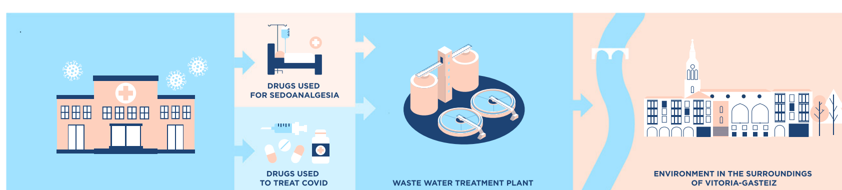
S. Domingo-Echaburu [a], M. Irazola [b,c,d], A. Prieto [e,f], B. Rocano [e], A. Lopez de Torre-Querejazu [g], A. Quintana [h], G. Orive [i,j,k,l,m,*], U. Lertxundi [n,**]

[a] Osakidetza Basque Health Service, Debagoiena Integrated Health Organisation, Pharmacy Service, Nafarroa Hiribidea, 16, 20500 Arrasate, Gipuzkoa, Spain
[b] Biocruces Bizkaia Health Research Institute, ES48903 Barakaldo, Biscay, Spain
[c] Department of Analytical Chemistry, University of the Basque Country, ES48940 Leioa, Biscay, Spain
[d] Research Centre for Experimental Marine Biology & Biotechnology, ES48620 Plentzia, Biscay, Spain
[e] Department of Analytical Chemistry, Faculty of Science and Technology, University of the Basque Country, Bilbao, Spain
[f] Research Centre for Experimental Marine Biology and Biotechnology, University of the Basque Country (PiE-UPV/EHU), Plentzia, Basque Country 48620, Spain
[g] Pharmacy Service, Araba-Integrated Health Care Organization, Santiago Hospital, Vitoria-Gasteiz, Alava, Spain
[h] Pharmacy Service, Araba Integrated Health Care Organization, Txagorritxu Hospital, Vitoria-Gasteiz, Alava, Spain
[i] NanoBioCel Group, Laboratory of Pharmaceutics, School of Pharmacy, University of the Basque Country UPV/EHU, Paseo de la Universidad 7, Vitoria-Gasteiz 01006, Spain
[j] Biomedical Research Networking Centre in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN), Vitoria-Gasteiz, Spain
[k] University Institute for Regenerative Medicine and Oral Implantology - UIRMI (UPV/EHU-Fundación Eduardo Anitua), Vitoria, Spain
[l] Singapore Eye Research Institute, The Academia, 20 College Road, Discovery Tower, Singapore
[m] Bioaraba, NanoBioCel Research Group, Vitoria-Gasteiz, Spain
[n] Bioaraba Health Research Institute, Osakidetza Basque Health Service, Araba Mental Health Network, Araba Psychiatric Hospital, Pharmacy Service, c/Alava 43, 01006 Vitoria-Gasteiz, Alava, Spain

HIGHLIGHTS

- Vitoria-Gasteiz was one of the hardest hit cities in the world during the COVID-19 first wave.
- The use of certain drugs in hospital was multiplied by 25 during that period.
- We report the first positive detection of hydroxychloroquine in the environment.
- We report the second positive detection of lopinavir in the environment.
- Low risk for lopinavir, ritonavir and hydroxychloroquine. Moderate for azithromycin.

GRAPHICAL ABSTRACT



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ABSTRACT

The city of Vitoria-Gasteiz was one of the probable first entrances of the SARS-CoV2 in Spain, one of the worst affected countries in the world during the first COVID 19 wave. Driven by the urgency of the situation, multiple drugs with antiviral activity were used off label. Sadly, most of these treatments were of little or no benefit and thus, the number of patients suffering from COVID-19 attended in intensive care units (ICUs) multiplied. After being administered to patients, a variable proportion of these drugs reach the environment where they may have detrimental effects, although this aspect is usually ignored by healthcare professionals. In this study we measured the patterns of hospital drug use in the city of Vitoria-Gasteiz (Spain) during the first COVID-19 wave pandemic, focusing on those with antiviral activity

* Correspondence to: G. Orive, NanoBioCel Group, Laboratory of Pharmaceutics, School of Pharmacy, University of the Basque Country UPV/EHU, Paseo de la Universidad 7, Vitoria-Gasteiz 01006, Spain.
** Correspondence to: U. Lertxundi, Bioaraba Health Research Institute, Araba Mental Health Network, Araba Psychiatric Hospital, Pharmacy Service, c/Alava 43, 01006 Vitoria-Gasteiz, Alava, Spain.
E-mail addresses: gorka.orive@ehu.es (G. Orive), unax.lertxundietxebarria@osakidetza.net (U. Lertxundi).

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and those used in the ICUs. Subsequently, we measured concentrations of selected drugs in the city's wastewater treatment plant influent and effluent and estimated the potential risk for the environment. The hospital use of certain antivirals and drugs used for sedo-analgesia were dramatically increased during the first wave (cisatracurium was multiplied by 25 and lopinavir/ritonavir by 20). A mean of 1.632 daily defined doses of hydroxychloroquine were used during the period of February–May 2020. In this study we report the first positive detection of hydroxychloroquine ever in the environment. We also show the second positive report of lopinavir. Low risk was estimated for hydroxychloroquine, lopinavir and ritonavir (Risk quotients (RQ) <1), and medium risk for azithromycin (RQ 0f 0.146).

1. Introduction

Spain was hit hard by the COVID-19 first wave, being considered by many as one of the worst affected countries in the world (García-Basteiro et al., 2020). Phylo-geographic analysis have shown that the city of Vitoria-Gasteiz was one of the probable first entrances of the SARS-CoV2 in the country (Gómez-Carballa et al., 2020). With 216% intensive care unit (ICU) capacity expanded by March 18th, 2020, our city was one of the hardest hit among one of the most dramatically affected regions in the world (Barrasa et al., 2020).

In those times of scientific uncertainty, and driven by the urgency of the situation, many different drugs with antiviral activity were desperately administered to save patients´ lives. Sadly, many of this off-label treatments showed little or no benefit (Boulware et al., 2020, Skipper et al., 2020, Cavalcanti et al., 2020, RECOVERY Collaborative Group, 2020) and some of them were even harmful for patients (Eftekhar et al., 2021). Moreover, as the number of patients suffering from COVID-19 attended in ICUs multiplied, the amount of sedo-analgesics and neuromuscular blocking agents also incremented significantly (Corregidor-Luna et al., 2020).

One aspect that has been vastly ignored by healthcare providers is the environmental impact of many of the drugs used during the pandemic. After being administered to patients, a variable proportion of these drugs reach the environment where they may have detrimental effects (Tarazona et al., 2021, Farias et al., 2020, Elsaid et al., 2021). The ecotoxicity of some pharmaceuticals used for COVID-19, e. g. azithromycin and ivermectin is reasonably well addressed. Azithromycin is particularly toxic for cyanobacteria, and ivermectin shows a moderate toxicity for fish and algae and an extremely high toxicity for invertebrates (Swedish environmental classification of pharmaceuticals: hydroxychloroquine, n.d.).

In this study we aimed to measure the patterns of hospital drug use in Vitoria-Gasteiz during the first COVID-19 wave pandemic, focusing on those with antiviral activity and those used in the ICUs. Subsequently, we tried to measure these drugs concentrations in the city's wastewater treatment plant influent and effluent, to assess their potential ecotoxicological effects.

2. Methods

2.1. Hospital drug consumption during the COVID-19 first wave in Vitoria-Gasteiz

Vitoria-Gasteiz is the capital city of the Basque Country, an autonomous region located in Northern Spain, where two public acute-care hospitals pertaining to the Araba Integrated Healthcare organization (Txagorritxu and Santiago) attend a population of 248.087 (EUSTAT, 2021). Drug consumption data was obtained from SAP program (an enterprise application software), which is available for Osakidetza, the public health service provider since 1998. This database contains information about all drug consumption and cost for all public healthcare hospitals in the autonomous region. Drug consumption data was obtained for the first wave period (February–May 2020), and compared with the same period form the two previous years, i.e.: 2018 and 2019.

Studied drugs were those that were directly used to treat COVID-19 because of their antiviral activity, including hydroxychloroquine and lopinavir/ritonavir, or their immunomodulatory properties, like the antibiotic azithromycin, baricitinib, tocilizumab, methylprednisolone and dexamethasone. Other included drugs were: loperamide, because of its wide use to treat lopinavir/ritonavir provoked diarrhea; neuromuscular blocking agents used in ICUs like cisatracurium and rocuronium; sedo-analgesic drugs like intravenous midazolam, fentanyl, remifentanil and propofol; antibiotics like levofloxacin and ceftriaxone; bronchodilators like ipratropium and salbutamol; and low-molecular-weight heparin enoxaparin.

After obtaining raw consumption data, the number of daily defined doses (DDD) for individual drugs were calculated (WHO ATC, 2021). In the case of cisatracurium, no DDD is available, so consumption was arbitrarily normalized considering 20 mg.

2.2. Waste-water treatment plant influent and effluent concentrations

One liter 24 h composite samples (200 mL every hour) of both influent and effluent waste-water from the municipal WWTP of the city of Vitoria-Gasteiz (Crispijana) were collected from April 28th to July 13th in polypropylene bottles.

Data on chemical oxygen demand, biological oxygen demand, total nitrogen, total phosphorus and daily flow in the influent of the WWTP and the date of each sample are available as supplementary material (Table S1).

A total of 16 samples were subsequently transported to the laboratory at the University of the Basque Country (UPV/EHU) and stored at −20 °C until their processing. Water was filtered (cellulose filters 0.7 μm, 90 mm, Whatman) and spiked with a deuterated standard mix and processed according to a method previously validated (González-Gaya et al., 2021). Briefly, three replicates of 250 mL (effluent) and 100 mL (influent) were extracted using in-house made SPE cartridges containing 100 mg of cationic exchange (ZT-WCX), 100 mg of anionic exchange (ZT-WAX) and 300 mg reverse phase (HRX) sorbents from bottom to top. Conditioning was done with 10 mL of MeOH: ethyl acetate (1:1, v/v) and 10 mL Milli-Q water, and after sample loading, the cartridges were eluted with 12 mL of MeOH: ethyl acetate (1:1, v/v) containing 2% ammonia and 12 mL of MeOH: ethyl acetate (1:1, v/v) 1.7% formic acid. Both extracts were combined, evaporated on a Turbovap (Zymark, Hopkinton, USA) at 40 °C under a gentle N_2 flow and reconstituted on 250 μL MeOH: Milli-Q water (1:1, v/v). Final extracts were filtered with syringe filters (PP, 0.22 μm, 13 mm, Jasco Analítica, Madrid, Spain) onto amber chromatography vials and analyzed in a Thermo Scientific Dionex UltiMate 3000 UHPLC coupled to a Thermo Scientific Q Exactive Focus quadrupole-Orbitrap mass spectrometer (UHPLC-q-Orbitrap) equipped with a heated ESI source (HESI, Thermo-Fisher Scientific, CA, USA) at the conditions previously reported (González-Gaya et al., 2021).

In the validation of the analytical procedure used in this work satisfactory results were obtained and are available as supplementary material (Table S3). Eight calibration levels within 0.1 ng/g and 50 ng/g were injected in triplicate for the determination of instrumental LODs and LOQs. Instrumental LODs were estimated as the lowest concentration detected in the three injection replicates, and in the case of instrumental LOQs, as the lowest concentration detected with a relative standard deviation (RSD) of less than 30% and a closeness to the true concentration values of more than 70%. The procedural LODs and LOQs were stablished as the theoretical concentration measurable and quantifiable in a water sample (a mixture of different wastewater samples) taking into account the instrumental LODs and LOQs, the absolute recoveries and the preconcentration factor of the target compounds.

The relative recovery was calculated as the percentage ratio of the compound concentration estimated from the internal calibration to the theoretical concentration, using six Milli-Q water samples spiked with all compounds of interest.

The RSD values of the three replicates analyzed ranged between 1 and 30%, within the standards defined by the European Commission, which indicates an RSD value ≤30% as acceptable (EUR-LEX, 2002).

2.3. Reported environmental concentrations for selected drugs in the literature and ecotoxicity data

To find out reported environmental concentrations of the drugs used to treat COVID-19 inpatients in the literature, we used The Pharmaceutical Database published by the German Environment Agency – Umweltbundesamt (UBA. German Environment Agency, 2019).

Ecotoxicity data (Predicted no-effect concentration: PNEC) was looked for each individual pharmaceutical. When no data was available, Ecological Structure Activity Relationship tool (ECOSAR v2.0) from the United States Environment Protection Agency was used (ECOSAR, 2021) was used to estimate PNECs. Then, a factor of 25 was used to correct the impact of dilution of the effluent in surface water (Keller et al., 2014).

3. Results

3.1. Hospital drug consumption during the COVID-19 first wave in Vitoria-Gasteiz

Fig. 1 illustrates the drugs which consumption was more drastically incremented. Interestingly, the average use of cisatracurium was multiplied by 25 and lopinavir/ritonavir by 20. Although the hospital use of hydroxychloroquine was not registered before the first wave, a mean of 1.632 DDD use during the period of February–May 2020 was recorded. A complete list of the detailed consumption of the selected drugs during the first wave pandemic compared to the same period during the two previous years can be consulted as supplementary material (Table S2).

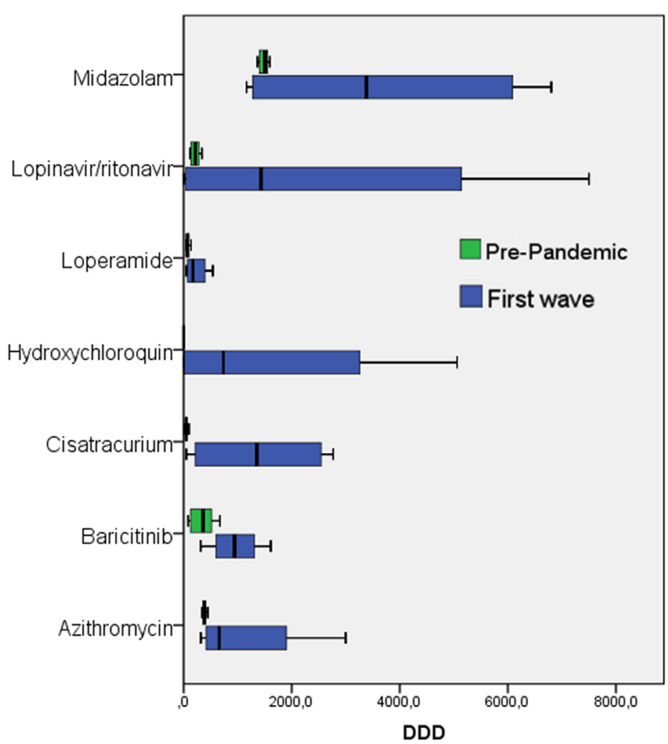

Fig. 1. Hospital drug consumption in daily defined doses (DDDs) *cisatracurium, normalized 20 mg. Individual values can be consulted in the Table S2 of the supplementary material.

3.1.1. Waste-water treatment plant influent and effluent concentrations

Concentrations of selected drugs detected in the WWTP influent and effluent are available in Fig. 2.

3.2. Concentrations and ecotoxicity

Table 1 shows a summary of the available information in the literature about the presence in different environmental matrices of some of the most relevant drugs used during the first COVID-19 wave, and ecotoxicity data (PNECs and RQ).

4. Discussion

Vitoria-Gasteiz was one of the most affected cities early in the first COVID-19 wave pandemic. On March 18, 2020, a 216% expansion in ICUs capacity was required to attend critically ill patients.

In this study we have shown that the use of cisatracurium was multiplied by 25, and lopinavir/ritonavir by 20, compared with pre-pandemic period. The highest lopinavir/ritonavir/use was registered on March, with 7.503 DDDs. That would equal to 250 patients taking a daily lopinavir/ritonavir dose during that month (approximately 1/1.000 persons from Vitoria-Gasteiz was hospitalized and taking this antiviral drug on March 2020).

For most of these drugs, there is scarce information about their potential deleterious effects in the environment. Tarazona et al. predicted the potential ecotoxicological consequences of some relevant drugs used during this pandemic (Tarazona et al., 2021). Quantitative structure-activity relationship (QSAR) estimations predicted that hydroxychloroquine (a metabolite of the antimalarial chloroquine) is slightly less toxic than chloroquine for aquatic organisms. So the authors extrapolated the chloroquine a PNEC value (120 μg/L) to hydroxychloroquine. An assessment factor (AF) of 100 was used to derive this value from algal toxicity data. Other authors report that the most sensitive organism to this antimalarial drug is the

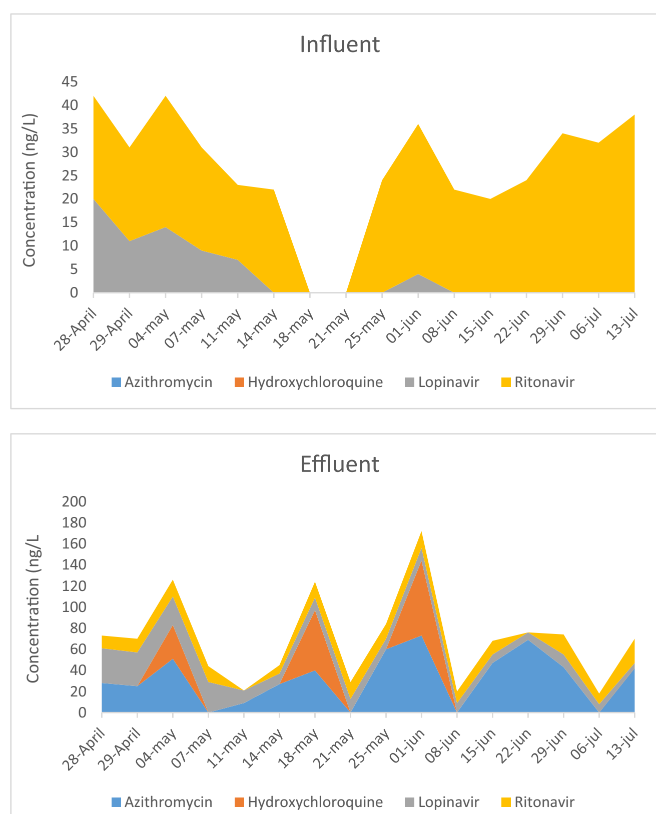

Fig. 2. Concentrations of selected drugs in the WWTPs influent and effluent.

Table 1
Information about the presence in the environment of the most relevant drugs used during the first wave and expected ecotoxicity.

Drug	N° of studies with positive detection	Highest ever recorded MEC† (μg/L)	Environmental matrix-location	UN Region-Country	Citation	Maximum MEC in Vitoria-Gasteiz (μg/L)	PNEC (μg/L)	RQ*
Hydroxychloroquine	None	–		–	–	0.071	85.8[a]	3.3×10^{-5}
Lopinavir	1	0.305	Surface Water - River/Stream -Hartbeespoort Dam, Meerhof, South Africa	Africa- South Africa	Wood et al., 2015	0.033	4.5[b]	2.9×10^{-3}
Ritonavir	5 (all from Switzerland)	0.12	WWTP Vidy Lausanne, WWTP influent	Western Europe-Switzerland	Margot et al., 2011	0.033	2.9[c]	4.6×10^{-3}
Cisatracurium	None	–	–	–	–	–	65[d]	–
Azithromycin±	105	16.6	Surface Water - Aquaculture Mar Menor Lagoon	Western Europe-Spain	(Moreno-González et al., 2014)	0.073	0.02[e]	0.146

WWTP: wastewater treatment plant; MEC: Measured environmental concentration; PNEC: Predicted no effect concentration; RQ: Risk quotient. †According to the German Environmental Agency's Pharmaceutical Database ±included in the EU Watch List monitoring program under the Water Framework Directive. *A dilution factor of 25 was considered (Keller et al., 2014). [a]NOEC 21 days, reproduction, *Daphnia Magna* AF of 100 (Swedish environmental classification of pharmaceuticals: hydroxychloroquine, n.d.). [b]ECOSAR v 2.0. ChV, Daphnids. [c]ECOSAR v 2.0. ChV, Fish, [d] For atracurium· ECOSAR v 2.0. ChV, [e]Fish Grow inhibition test (OECD 201), *M. aeruginosa*. NOEC with an AF of 10. (Tell et al., 2019).

crustacean (*Daphnia magna*), with a no observed effect concentration (NOEC 21 days, reproduction) of 85.8 μg/L (Swedish environmental classification of pharmaceuticals: hydroxychloroquine, n.d.). The same authors report that this drug is s potentially persistent (0% degradation in 28 days). We found a maximum concentration of 0.071 μg/L, which is below the 2 μg/L European Medicines Agency (EMA) default estimation (1% population treated). As far as we are concerned, in this study we provide the first detection of this drug in a WWTP effluent. Expected environmental risk appears to be low, with a RQ <1 (Table 1).

There is much more information for the macrolid antibiotic azithromycin, which is included in the European monitoring program under the Water Framework Directive (Gomez Cortes et al., 2020). The German Environmental Agency's Pharmaceutical Database contains more than one hundred reports of positive detections for this drug, which has shown to be particularly toxic to cyanobacteria *(Microcystis aeruginosa)* with a PNEC of 0.02 μg/L (OECD grow inhibition test, NOEC with an AF of 10) (Tell et al., 2019). This value is below the higher measured concentration in our study, which was 0.073 μg/L indicating a potential risk for the environment (Risk quotient RQ = 0.146).

Regarding the antiviral lopinavir, we found a concentration of 0.033 μg/L. The Swedish environmental classification of pharmaceuticals states that "*lopinavir has high potential for bioaccumulation*" (log Dow = 4.7, which is >4) (Swedish environmental classification of pharmaceuticals: lopinavir, n.d.). So far, there is just one additional report of its presence in the environment in the German database from South Africa. The study of Tarazona et al. (2021) clearly reflects the scarce available ecotoxicological information on these medicinal products (with the remarkable exception of oseltamivir). They concluded that "*despite the uncertainties in the extrapolation of the ecotoxicity data, available information suggests that the predicted concentrations for the antiviral and pharmacokinetic boosters are in the range of the generic PNEC values for antivirals, and that specific attention is required for sublethal effects on fish*". However, we found no experimental data regarding lopinavir ecotoxicity. ECOSAR tool v2.0 predicts a chronic value (geometrical mean of the NOEC and LOEC) of 4.5 μg/L for *Daphnids* (ECOSAR, 2021). Thus, the RQ for this drug is predicted to be low (RQ = 2.9×10^{-3}). In the case of ritonavir, the same tool predicts a chronic value of 2.5 μg/L for fish (RQ = 4.6×10^{-3}).

We believe that the potential ecological impact of antivirals on viruses present in the environment has not been sufficiently addressed so far. Very recently Kuroda and co-workers predicted the occurrence, ecotoxicological risk and acquired resistance of antivirals associated with COVID-19 in environmental waters (Kuroda et al., 2021). They suggested that the removal efficiencies at conventional WWTPs will remain low for half of the substances, and that high concentrations might be present in effluents and thus persist in the environment. They also estimated a high ecotoxicological risk in receiving river waters for lopinavir and ritonavir, and medium risk for hydroxychloroquine among others. Finally, they suggested that the potential of wildlife acquiring antiviral drug resistance was low (Kuroda et al., 2021). However, they did not acknowledge the possibility of bioaccumulation through the food-web (Orive and Lertxundi, 2020a, 2020b; Previšić et al., 2021).

Tarazona et al. highlighted that a high environmental risk was expected for ivermectin (Tarazona et al., 2021), a drug that was not used in our setting (Domingo-Echaburu, 2021).

One important issue is that the potentially prolonged spikes in freshwater drug concentrations that pandemic brings are not considered in the environmental risk assessments (ERA) presented to healthcare authorities such as the EMA (2019).

Some issues have to be taken into account when interpreting our results. Sadly, WWTP influent and effluent samples were not taken on the time of maximum drug use. Besides, for all these drugs, it should be considered that the use in COVID-19 patients should be added to environmental emissions from current uses.

The results obtained in the analysis of the selected drugs shown in Fig. 2 follow the same pattern. The first sample was collected near the peak incidence (early April) and a decrease in concentration can be observed as time progresses, which coincides with the gradual decrease in incidence observed in the Basque Country. An increase in the concentration of the compounds can also be observed from June onwards. This is the period in which the incidence of the disease began to gradually increase until it reached its maximum at the beginning of September (Department of Health, 2021).

In terms of interpreting the concentrations of the compounds there is also an issue to be considered. It is noteworthy that the compounds had a higher concentration in effluent than in influent. This is striking because, in theory, the concentration of the different compounds present in the influent of the WWTP should be higher than in the effluent, but this can be explained by two arguments. First, the water sampled in the effluent is not the same water body from which the influent sample was taken and therefore the concentrations are not always correlated. Second, influent samples are more complex to analyse due to the high matrix effect. This may even lead to the non-detection of certain compounds if they are present at very low concentrations.

With regards to ecotoxicity data, there is scarce information except for azithromycin. Data for lopinavir and ritonavir was predicted with ECOSAR.

5. Conclusion

Hospital use of antivirals and sedo-analgesic drugs was dramatically increased during the first COVID 19 wave in Vitoria-Gasteiz. In this study we report the first ever positive detection of hydroxychloroquine and the second positive detection of lopinavir in the environment. Low risk was estimated for all drugs except azithromycin, for which the risk was moderate.

CRediT authorship contribution statement

Saioa Domingo-Echaburu: writing original draft. Amaia Lopez de Torre-Querejazu: Investigation, writing- review & editing. Ainhoa Quintana: Investigation, writing- review & editing. Ailette Prieto: Investigation, writing- review & editing. Mireia Irazola: Investigation, writing- review & editing. Bryan Rocano: Investigation, writing- review & editing. Gorka Orive: Investigation, writing- review & editing. Unax Lertxundi: Investigation, writing- review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2022.153122.

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